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Reference intervals for venous blood gas measurement in adults

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Abstract

Objectives: Venous blood gas (VBG) analysis is becoming a popular alternative to arterial blood gas (ABG) analysis due to reduced risk of complications at phlebotomy and ease of draw. In lack of published data, this study aimed to establish reference intervals (RI) for correct interpretation of VBG results.

Methods: One hundred and 51 adult volunteers (101 females, 50 males, 18–70 years) were enrolled after completion of a health questionnaire. Venous blood was drawn into *safe*PICO syringes and analysed on ABL827 blood gas analyser (Radiometer Pacific Pty. Ltd.). A non-parametric approach was used to directly establish the VBG RI which was compared to a calculated VBG RI based on a meta-analysis of differences between ABG and VBG

Results: After exclusions, 134 results were used to derive VBG RI: pH 7.30–7.43, partial pressure of carbon dioxide (pCO_2) 38–58 mmHg, partial pressure of oxygen (pO_2) 19–65 mmHg, bicarbonate (HCO_3–) 22–30 mmol/L, sodium 135–143 mmol/L, potassium 3.6–4.5 mmol/L, chloride 101–110 mmol/L, ionised calcium 1.14–1.29 mmol/L, lactate 0.4–2.2 mmol/L, base excess (BE) –1.9–4.5 mmol/L, saturated oxygen (sO_2) 23–93%, carboxyhaemoglobin 0.4–1.4% and methaemoglobin 0.3–0.9%. The meta-analysis revealed differences between ABG and VBG for pH, HCO_3–, pCO_2 and pO_2 of 0.032, –1.0 mmol/L, –4.2 and 39.9 mmHg, respectively. Using this data along with established ABG RI, calculated VBG RI of pH 7.32–7.42, HCO_3– 23 – 27 mmol/L, pCO_2 36–49 mmHg (female), pCO_2 39–52 mmHg (male) and pO_2 43–68 mmHg were formulated and compared to the VBG RI of this study.

Conclusions: An adult reference interval has been established to assist interpretation of VBG results.

Keywords: blood gas analysis; reference intervals; venous blood.

Introduction

In healthcare, blood gas analysis commonly refers to measurement of pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), lactate and calculation of bicarbonate (HCO_3–) and base excess (BE). Improvements in analytical instrumentation have allowed modern blood gas analysers to also measure total haemoglobin and various haemoglobin fractions, electrolytes (sodium, potassium, chloride, magnesium and calcium ions), glucose and creatinine. Blood gas analysis offers important and timely clinical information regarding a patient's metabolic and respiratory function that is central for the diagnosis, treatment and monitoring of various conditions. Arterial blood gas (ABG) analysis is a valuable tool in assessing patients, especially in emergency and critical care settings, although, there are risks with arterial sampling, which include haematoma, infection at puncture site, arterial vasospasm and arterial thrombosis resulting in peripheral nerve damage and ischaemic injury to digits [1]. Venous blood gas (VBG) analysis has therefore been suggested as an alternative and it is becoming popular especially in emergency care settings. Venous sampling is relatively simple to perform, and requires minimal staff training in comparison with ABG collection [2]. Furthermore, it is less painful for patients, and exposes both the patient and the collector to less risk and complications.

Although several studies have compared ABG and VBG results, VBG reference intervals (RI) are still to be

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established using direct methods. The aim of this study was to support the correct interpretation of results by direct estimation of reference intervals for the most commonly used venous blood gas parameters. We compared our directly determined VBG reference intervals with those indirectly determined by adjusting ABG reference intervals based on estimated differences in blood gas parameters between arterial and venous blood.

Materials and methods

The EP28-A3c Clinical Laboratory Standards Institute (CLSI) document for defining, establishing, and verifying reference intervals in the clinical chemistry laboratory was used as a guide during this study [3].

Selection of reference individuals

Healthy adults or individuals whose condition was unlikely to affect blood gases and acid-base balance were enrolled into the study. The inclusion criteria involved non-smoking status (minimum of 12 months without smoking), no prior diagnosis or treatment of any respiratory illness, type 1 diabetes, bulimia or anorexia nervosa in the past 12 months, and no vomiting or diarrhoea in the past week. As samples were required after an overnight fast, vulnerable groups, including the elderly (>70 years) and pregnant women, were not invited to participate. Compliance with the above criteria was established using a health questionnaire on which study participants' weight and height were also recorded. Participants were volunteers employed by New South Wales (NSW) Health in Sydney, Australia. Informed consent was obtained from all individuals included in this study.

Preanalytical and analytical methods

Fasting venous blood sample was collected by a trained and experienced phlebotomist into a *safe*PICO blood gas syringe (Radiometer Pacific Pty. Ltd.) via standard venepuncture from the antecubital fossa. Tourniquets were released within 1 min of application to prevent preanalytical errors such as potential haemolysis and increase in lactate levels. Visible air bubbles were expelled immediately after collection via the syringes' vented cap to avoid errors in pCO_2, pO_2 and saturated oxygen (sO_2). The VBG samples were then mixed thoroughly using the built-in mixing ball and analysed within 15 min of collection on ABL827 blood gas analysers (Radiometer Pacific Pty. Ltd.). Parameters included for statistical analysis were pH, pCO_2, pO_2, bicarbonate, lactate, sodium (Na^+), potassium (K^+), chloride (Cl^-), ionised calcium (Ca^{2+}), BE and sO_2, carboxyhaemoglobin and methaemoglobin. The ABL827 blood gas analyser uses potentiometry for measuring pH, pCO_2, Na^+, K^+, Cl^- and Ca^{2+}. Lactate and pO_2 were measured by amperometry. Optical measurement principles were applied to sO_2, carboxyhaemoglobin and methaemoglobin testing. Bicarbonate and base excess were automatically calculated using the Henderson-Hasselbalch equation and the Siggaard-Andersen nomogram respectively.

Ethics approval

This study was compliant with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration. The study has been approved by the Human Research Ethics Committee of Charles Sturt University (ethics approval number H16177).

Systematic review

A literature search was performed from 1970 to 2019 to identify original studies, literature reviews and meta-analyses comparing ABG and VBG in healthy adult humans or in those with any type of clinical disorder. Electronic data bases (PubMed and Google Scholar) were searched using a combination of the following terms: venous blood gas, arterial blood gas, comparison, agreement and correlation. The reference lists of publications and citation tracking were used for the identification of additional relevant papers. Only studies that compared venous to arterial blood gases in adult human subjects were included in the meta-analysis. Included studies also stated the sample size and reported both the mean and standard deviation (SD) for one or more parameter (pH, pCO_2, pO_2, HCO_3– and lactate) for paired, sequentially collected venous and arterial blood samples. Sample size, paired (VBG and ABG) pH, pCO_2, pO_2, HCO_3– and lactate mean and SD values were extracted from all eligible publications.

Statistical analyses

Reference intervals were calculated using the non-parametric approach based on the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine [3]. Screening for outlier exclusion was undertaken using the Dixon-Reed test [4]. Sex-dependent differences were explored using a Mann–Whitney U test [5]. Age-dependent differences were assessed using analysis of variance [5] or the Welch test [6] in the presence of significant heteroscedasticity. Where differences were found for a given analyte, age and or sex partitioned reference intervals were calculated as indicated using the robust method [3] as implemented in the R Reference Intervals package. The data are presented as 2.5 – 97.5 percentile ranges with 90th percentile confidence intervals.

Meta-analysis was conducted to produce a pooled mean estimated difference between venous and arterial blood gas parameters. Studies that reported sample size, mean difference between ABG and VBG and its standard deviation (SD) for at least one of the parameters, i.e. pH, pCO_2, pO_2, and HCO_3– were used in the meta-analysis. The combined mean difference and its SD were calculated if more than two sub-study populations were involved in one study. Meta-analysis for each parameter was performed using random effect models to pool the results. Meta-analysis was carried out using R version 3.6.1. Exploratory data analysis and calculation of reference intervals were undertaken using R version 4.0.2 and Analyse-it v2.2 for Microsoft Excel.

The Knapp-Hartung approach [7] was applied to account for heterogeneity between studies. Between-study heterogeneity was evaluated using chi-square tests and I^2 statistics [8]. The potential for publication bias for each meta-analysis was assessed by inspection of funnel plots and statistical tests based on weighted linear regression of the intervention effect on its standard error [9]. All statistical tests were two-sided and were evaluated at a significance level of 0.05.

We then compared our findings to that of previously published similar meta-analyses. The summary estimate for ABG-VBG difference derived from our meta-analysis for each measurand (except for lactate) was used to calculate a theoretical VBG RI from ABG RI published by the manufacturer [10].

Results

Venous blood gas reference intervals

A total of 151 NSW Health employees volunteered to participate in the study of which 17 indicated that they had smoked cigarettes, cigars, e-cigarettes or similar in the previous 12 months. After removal of these participants 134 VBG results were included in the analysis for the establishment of the VBG RI. The health questionnaires revealed one volunteer suffering from a respiratory illness at the time of collection and another had been treated for a respiratory illness in the previous 12 months. Both individuals were already excluded due to their smoking status.

The number of males and females in each age band is shown in Table 1.

Only a single outlier was identified for bicarbonate by the Dixon-Reed test. All results for all other analytes were included in the analysis.

While there was significant imbalance between a number of females and males in the study, statistically significant sex-dependent differences were found for pCO_2, bicarbonate, potassium, chloride, and calcium. Venous pCO_2 was lower in females (36–56 mmHg) than males (38–60 mmHg). However, the confidence limits for the upper and lower reference limits for both males and females included those for the combined reference interval (37–58 mmHg), and therefore the combined reference limit was considered appropriate. In all other cases the differences were small and a combined reference interval was considered reasonable.

As shown in Table 1 the number of subjects was not smoothly distributed among the age bands. In order to get sufficient numbers in each band the first two and last two age bands were combined before assessing for age-dependent differences. Statistically significant age-dependent differences were found for pCO_2, bicarbonate, chloride, and lactate. Again, the differences were small, and combined with the uncertainty in the partitioned reference intervals, a combined reference interval was considered appropriate in all cases.

The VBG RI obtained in our reference population are presented in Table 2.

Table 1: Distribution of subjects by age and sex.

Age band, years	Female	Male	Total
18 – 25	6	2	*8*
26 – 35	35	16	*51*
36 – 45	14	6	*20*
46 – 55	24	12	*36*
56 – 65	10	5	*15*
66 – 70	3	1	*4*
Total	92	42	134

Systematic review and meta-analysis of ABG-VBG differences

The literature review revealed 21 original studies comparing ABG and VBG that met inclusion criteria [1, 11–30], as well as 8 literature reviews and/or meta-analyses [31–37].

All original studies identified had collected consecutive ABG and VBG samples from a population of adults presenting with various clinical problems including diabetic ketoacidosis (DKA) [17, 25], chronic obstructive pulmonary disease (COPD) [11, 22, 24] or were critically ill in intensive care or in an emergency department (ED) [1, 12, 16, 18]. Due to the clinical states of the subjects involved in the studies used in the meta-analyses, some subjects received supplemental oxygen or mechanical ventilation at the time of sample collection. Results of the meta-analyses for ABG-VBG differences are presented by forest plots for pH, HCO_3–, pCO_2 and pO_2 (Figure 1). Twenty-one studies were included for summarising the mean difference for pH (Figure 1A). There was evidence of heterogeneity between studies (I^2=96.7%, p<0.001). Overall mean difference was 0.032 (95% CI: 0.026–0.037). There was no evidence of publication bias for the overall analysis (p=0.21).

A total of 16 studies were included in the meta-analysis for ABG-VBG differences for HCO_3– (Figure 1B). There was evidence of heterogeneity between studies (I^2=90.4%, p<0.001). Overall mean difference was –1.08 mmol/L (95% CI: –1.33 to –0.84). There is evidence of publication bias for the overall analysis (p=0.002).

Nineteen studies were used for a summary estimate of ABG-VBG differences for pCO_2 (Figure 1C). There was evidence of heterogeneity between studies (I^2=97.8%, p<0.001). Overall mean difference was –4.35 mmHg (95% CI: –5.57 to –3.14). There is evidence of publication bias (p=0.01).

A total of 13 studies were included in the meta-analysis for ABG-VBG differences for pO_2 (Figure 1D). There was evidence of heterogeneity between studies (I^2=98.1%,

Table 2: Venous blood gas reference intervals in healthy adults (n=134).

Measurand	Units	Reference interval (2.5–97.5 percentile)	90% Confidence interval Lower reference limit	90% Confidence interval Upper reference limit
pH		7.30 – 7.43	7.28 – 7.32	7.41 – 7.43
pO_2	mmHg	19 – 65	18 – 20	53 – 81
pCO_2	mmHg	38 – 58	37 – 38	57 – 59
Bicarbonate	mmol/L	22 – 30	22 – 23	29 – 30
Lactate	mmol/L	0.4 – 2.2	0.4 – 0.5	1.8 – 3.4
Sodium	mmol/L	135 – 143	134 – 136	142 – 144
Potassium	mmol/L	3.6 – 4.5	3.1 – 3.7	4.4 – 4.7
Chloride	mmol/L	101 – 110	100 – 101	109 – 112
Ionised Calcium	mmol/L	1.14 – 1.29	1.07 – 1.16	1.26 – 1.30
Base excess	mmol/L	−1.9 – 4.5	−3.0 - −1.0	4.1 – 4.8
Saturated oxygen	%	23 - 93	21 – 29	89 - 98
Carboxyhaemoglobin	%	0.4 – 1.4	0.4 – 0.5	1.3 – 1.5
Methaemoglobin	%	0.3 – 0.9	0.3 – 0.4	0.8 – 1.0

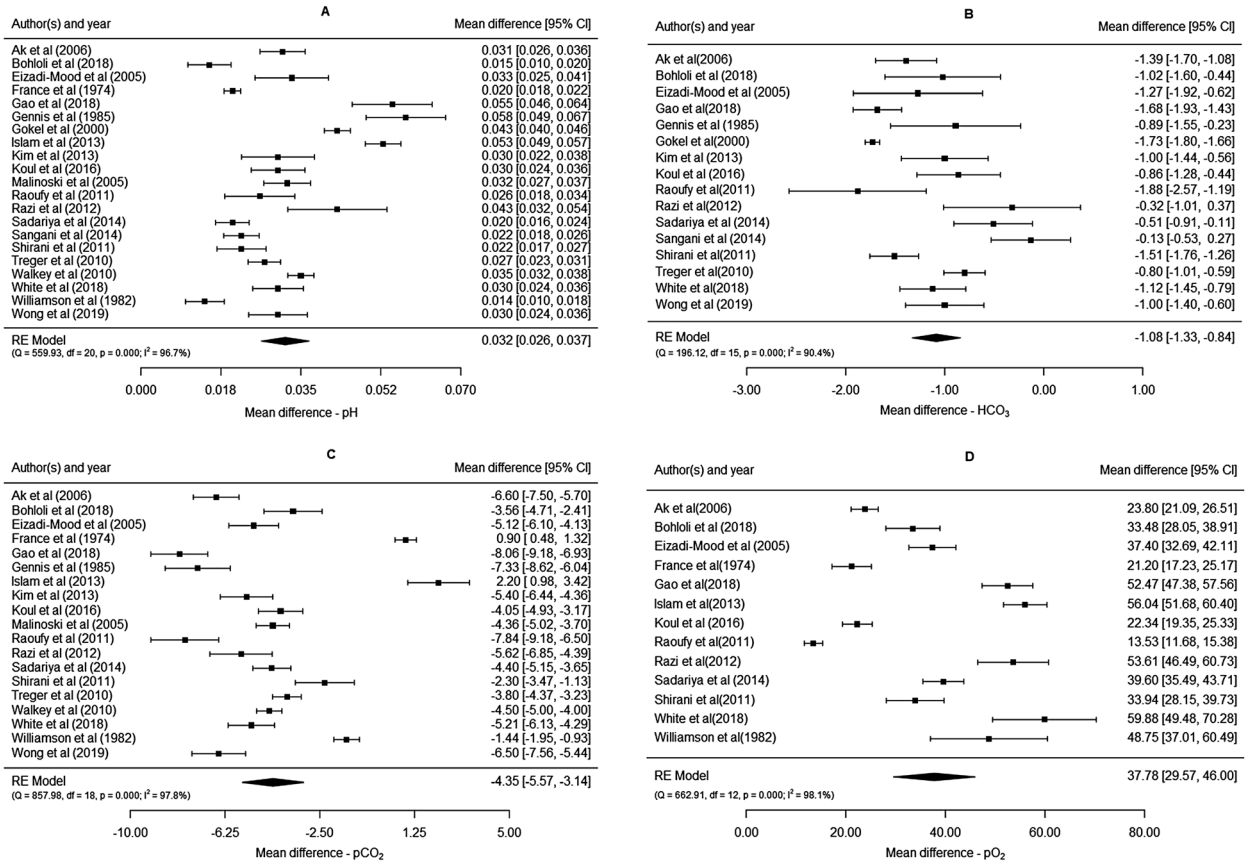

Figure 1: Meta-analysis of mean differences between arterial blood gas and venous blood gas parameters.

p<0.001). Overall mean difference was 38.78 mmHg (95% CI: 29.57 – 46.00). There is evidence of publication bias (p=0.001)

From the eight review articles assessing the agreement of ABG and VBG, identified during the initial literature review, seven performed meta-analyses. The summary

estimate for mean differences between ABG and VBG calculated in our meta-analysis was compared to similar data compiled in other meta-analyses (Table 3).

The theoretical VBG RI, calculated by using the pooled mean difference of ABG and VBG from the meta-analysis in Figure 1, and the ABG RI published by the manufacturer [10], are presented in Table 4. In the current systematic review, only one study reported results on lactate, therefore, the pooled mean difference for lactate from the meta-analysis performed by Bloom et al. [32] was used in the theoretical VBG RI calculation.

Venous blood gas RI established in the reference population of this study (Table 2) were then compared to the theoretical VBG RI presented in Table 4. Results are shown in Table 5.

Table 4: Theoretical venous blood gas reference intervals modelled from ABG-VBG differences applied to established arterial blood gas reference intervals.

Measurand	Published ABG RI [10]	Mean difference (ABG – VBG) (see Table 3 first line)	Theoretical VBG RI
pH	7.35 – 7.45	0.032	7.32 – 7.42
pO_2, mmHg	83 – 108	38.8	44 – 69
pCO_2, mmHg	Male 35 – 48	–4.4	39 – 52
	Female 32 – 45		36 – 49
Bicarbonate, mmol/L	22 – 26	–1.08	23 – 27
Lactate, mmol/L	0.5 – 1.6	–0.25[a]	0.8 – 1.9

ABG, arterial blood gas; VBG, venous blood gas; RI, reference intervals. [a]Bloom et al. (2014) meta-analysis value (30).

Discussion

To our knowledge this is the first published VBG reference interval study, therefore our findings presented in Table 2 could only be compared to theoretical VBG RI modelled from ABG-VBG differences published in systematic reviews and meta-analyses.

Our systematic review and meta-analysis used a total of 21 original studies comparing ABG and VBG; a greater number than other published meta-analyses that included a range of 3–18 studies. This may be due to various reviews focussing on a specific disease state such as COPD and DKA. Another reason could be that our systematic review included studies that compared blood gas results from both central and peripheral venous blood specimens whereas all the other reviews and meta-analyses used only studies that compared ABG with peripheral VBG. Analytical differences between various blood gas analysers may also account for the slight differences between the findings of various meta-analyses studying the difference between ABG and VBG. Although evidence of heterogeneity between studies was identified in our meta-analysis, we have applied a conservative approach (i.e. the Knapp-Hartung method) to account for it.

Table 5: Comparison of the venous blood gas reference intervals established in the current study to the theoretical reference intervals obtained by modelling.

Measurand	Current VBG RI study (data from Table 2)	Theoretical VBG RI (data from Table 4)
pH	7.30 – 7.43	7.32 – 7.42
pO_2, mmHg	19 – 65	44 – 69
pCO_2, mmHg	38 – 58	Male 39 – 52
		Female 36 – 49
Bicarbonate, mmol/L	22 – 30	23 – 27
Lactate, mmol/L	0.4 – 2.2	0.8 – 1.9

Table 3: Pooled mean differences between arterial and venous blood gas parameters in published systematic reviews and meta-analyses.

Difference (ABG – VBG)						
Study	**Health condition**	**pH**	**HCO_3^-, mmol/L**	**pCO_2, mmHg**	**pO_2, mmHg**	**Lactate, mmol/L**
Current meta-analysis	All	0.032	–1.08	–4.4	38.8	-
Bingheng et al. (2018)	AECOPD	0.020	–0.22	–2.9	13.1	-
Bloom et al. (2014)	All	0.033	–1.0	–4.4	-	–0.25
Bryne et al. (2014)	All	0.030	-	–3.9	36.8	-
Kelly (2013)	ED	0.034	–1.2	–6.2	-	-
Kelly et al. (2010)	ED	0.035	–1.4	–5.7	-	-
Lim et al. (2010)	COPD	0.028	–1.3	–5.9	18.7	-
Kelly et al. (2006)	DKA	0.020	-	-	-	-

ABG, arterial blood gas; VBG, venous blood gas; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; All, no specific disease state included in the study; DKA, diabetic ketoacidosis; ED, emergency department.

The ABG-VBG difference of pH calculated in 8 meta-analyses ranged from 0.020 to 0.035. The HCO_3– was also comparable with the majority of values ranging from –1.0 mmol/L to –1.4 mmol/L. There was some discordance in the calculated arterio-venous differences of pCO_2 with values ranging from –2.9 mmHg to –6.2 mmHg. Calculated differences for pO_2 were highly variable with values ranging from 13.1 to 38.8 mmHg, showing poor agreement in this parameter. This is understandable as pO_2 and pCO_2 are highly variable parameters in patients who suffer from respiratory or circulatory failure and greater arterio-venous differences were found in such cases in earlier studies [38]. Despite these differences in patient populations, analyser and sample types, our systematic review revealed very similar summary estimates for ABG – VBG differences to previously performed meta-analyses.

Comparison of the RI obtained in this study and through modelling (Table 5) shows satisfactory agreement, given the fact that most data on ABG-VBG differences were derived from acutely or critically ill patients rather than from healthy individuals. Reference intervals by modelling were overall comparable with the current VBG RI study revealing a pH of 7.30–7.43 and the modelling estimating a VBG RI of 7.32–7.42. Bicarbonate and lactate also showed similar results with the current RI study calculating 22–30 mmol/L and 0.4–2.2 mmol/L compared with estimated VBG RI of 23–27 mmol/L and 0.8–1.9 mmol/L, respectively.

Sex partitioning for ABG pCO_2 RI has been recommended by the manufacturer of the ABL blood gas analyser [10]. The male and female RI estimated by modelling are comparable to the results of our formal RI study, although the upper reference limit was higher in our RI study, which may be due to the fact that some older individuals in the study could have suffered from undiagnosed COPD. While statistically significant age- and sex-dependent differences were present in our data, the differences were small and there was significant uncertainty in the calculated partitioned reference intervals. A weakness of our study population was the lower ratio of males than females and the non-uniform distribution of various age groups in the reference population, which have limited our ability to calculate reliable age- or sex-specific reference intervals. Klaestrup et al. [39] found that females had lower arterial pCO_2 and higher pH and they attributed this to a higher respiratory rate that is more common in females than males. We also found a lower venous pCO_2 in females but no difference in pH. They also found that arterial pO_2 had an age-dependent decrease of 2.2 mmHg per decade. However, all these changes were considered small and clinically insignificant to justify age- and sex-specific RI.

Substantial differences were seen between study and theoretical RI of pO_2 at both the lower and upper limits. A systematic review has found VBG pO_2 an unreliable parameter in respiratory failure [33] and large variations and potential publication bias have been seen in all meta-analyses that estimated differences between ABG and VBG for this parameter. Therefore, the modelled RI may also be unreliable. Based on these findings, in agreement with earlier publications, we do not recommend reporting pO_2 and any RI for this measurand in VBG specimens. As sO_2 varies with the pO_2 in a nonlinear relationship, we also do not recommend reporting sO_2 and any RI for this measurand in VBG specimens.

Although theoretical RI, based on data from the meta-analyses, helped to strengthen some of the RI derived in our RI study, this modelling approach has several limitations. A major limitation of the meta-analysis was that many of the studies recruited critically ill patients in intensive care units (ICU) and EDs. Only 1 study [17] included a control group of healthy individuals, although the population size in this group was far less than seen in other studies on patients presenting with pathological conditions.

The use of ABG RI from the manufacturer, Radiometer [10], to model the VBG RI was also a limitation of the current analysis. The samples for the establishment of these ABG RI were whole blood, but there is no information pertaining to the collection of samples, characteristics of the reference population or the statistical analysis used to derive those RIs. Nevertheless, these ABG RIs are widely used by medical laboratories across the globe.

Although RIs for electrolytes, carboxyhaemoglobin and methaemoglobin could not be verified using the derived theoretical RI, comparison of the RIs for these parameters calculated in this study and ABG RIs published by Klaestrup et al. [39] shows good agreement. It is assumed that the electrolyte, carboxyhaemoglobin and methaemoglobin values do not differ significantly between arterial and venous blood. Results were comparable overall with the current VBG RI study calculating a sodium RI of 135–143 mmol/L, potassium RI of 3.6–4.5 mmol/L, chloride RI of 101–110 mmol/L and ionised calcium RI of 1.14–1.29 mmol/L and Klaestrup et al. [39] estimating an ABG RI of 136–141 mmol/L, 3.5–4.4 mmol/L, 102–110 mmol/L and 1.14–1.28 mmol/L, respectively. Klaestrup et al. [39] also reported a pH corrected ionised calcium RI of 1.16–1.28 mmol/L using the ABG mean pH of 7.40. When the ionised calcium is corrected in the current study using the VBG mean pH of 7.35, the RI becomes 1.16–1.28 mmol/L. Carboxyhaemoglobin and methaemoglobin also showed similar results with the current VBG RI study calculating

0.4–1.4% and 0.3–0.9% compared with Klaestrup et al. [39] ABG RIs of 0.9–1.7% and 0.5–1.3%, respectively. Base excess and saturated oxygen were not compared to published ABG RIs as base excess is affected by pH and pCO_2 and venous saturated oxygen cannot be compared to arterial saturated oxygen.

The RI derived from this study represents an adult population within Australia's metropolitan area for venous blood gas samples analysed on Radiometer's ABL800 series blood gas analysers. The locally determined RI may not be directly transferable in laboratories serving different populations or using different analytical instruments for blood gas analysis. The EP28-A3c CLSI guidelines [3] provide several alternatives to a full establishment of RI by way of transference testing using three different approaches; a subject assessment to compare reference populations; a statistical test on a small number of reference individuals (e.g. n=20); or an evaluation of a larger number of reference individuals but fewer than the minimum number (i.e. n=120) needed to perform a standard reference interval study. Laboratories willing to use the VBG RI established in this study are advised to use one of these methods for transference checking of our findings.

Conclusions

A reference interval has been established to assist interpretation of VBG results.

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